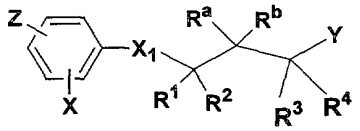
CLAIMS

We claim:

1. A compound of the formula



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wherein X_1 is O, $S(O)_n$, $-\overset{R^5}{\underset{|}{N}}-$, $co-\overset{R^5}{\underset{|}{N}}-$, or $-CH_2-$, with the proviso that when X_1 is $-CH_2-$, R_1 and R_2 are only halogen.

n is 0, 1 or 2;

R^a and R^b when taken together form an oxo (=O) group, or R^a and R^b are each independently hydrogen, OH, $OCOR^9$, NH_2, N_3, $NHCOOR^9$, $NHCOCOR^9$, $NHSO_2R^9$ or F;

X is H, CF_3, OCF_3, halogen, C_1–C_7 alkyl, C_2–C_7 alkenyl, C_2–C_7 alkynyl or C_3–C_7 cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by $COOR^8$, CN, $C(O)NR^6R^7$, PO_3R^8, SO_3R^8, heterocyclic, OR^8, SH, $S(O)_nR^9$, NR^6R^7, $NH(CO)NR^6R^7$, $NH(CO)OR^9$, aryl or heteroaryl, said aryl or heteroaryl being optionally substituted by one or two groups independently selected from NR^6R^7, OR^8, $COOR^8$, SO_3R^8, $OCOR^9$, PO_3R^8, $C(O)NR^6R^7$ or heterocyclic;

R^1 and R^2 are each independently H, halogen, OR^9, C_1–C_7 alkyl, C_2–C_7 alkynyl, C_2–C_7 alkynyl or C_3–C_7 cycloalkyl, said alkyl, alkenyl, alkynyl or

cycloalkyl group being optionally substituted by $COOR^8$, CN, $C(O)NR^6R^7$, PO_3R^8, SO_3R^8, heterocyclic, OR^8, SH, $S(O)_nR^9$, NR^6R^7, $NH(CO)NR^6R^7$, $NH(CO)OR^9$, $OC(O)OR^9$, aryl or heteroaryl, said aryl or heteroaryl being optionally substituted with one or two groups independently selected from NR^6R^7, OR^8, $COOR^8$, SO_3R^8, $OCOR^9$, PO_3R^8, $C(O)NR^6R^7$ or heterocyclic;

R^3, R^4 and Y are each independently H, halogen, OR^{10}, $S(O)_nR^{10}$, C_1–C_7 alkyl, C_2–C_7 alkenyl, C_2–C_7 alkynyl or C_3–C_7 cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by $COOR^8$, CN, $C(O)NR^6R^7$, PO_3R^8, SO_3R^8, heterocyclic, OR^8, SH, $S(O)_nR^9$, NR^6R^7, $NH(CO)NR^6R^7$, $NH(CO)OR^9$, $OC(O)OR^9$, aryl or heteroaryl, said aryl or heteroaryl being optionally substituted by one or two groups independently selected from NR^6R^7, OR^8, $COOR^8$, SO_3R^8, $OCOR^8$, PO_3R^8, $C(O)NR^6R^7$ or heterocyclic, with the proviso that not all of R^3, R^4 and Y may be the same halogen;

R^5, R^6 and R^7 are each independently H, C_1–C_7 alkyl, C_2–C_7 alkenyl, C_2-C_7 alkynyl or C_3–C_7 cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by $COOR^8$, CN, OR^8, NR^8R^9, SO_3R^8, PO_3R^8, halogen, aryl or heteroaryl, said aryl or heteroaryl being optionally substituted by one or two groups independently selected from $COOR^8$, SO_3R^8, PO_3R^8 or heterocyclic;

R^8 is H, C_1–C_7 saturated straight chain alkyl or cycloalkyl;

R^9 is same as R^8 but is not hydrogen;

R^{10} is C_1–C_7 alkyl, C_2–C_7 alkenyl, C_2–C_7 alkynyl or C_3–C_7 cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by $COOR^8$, CN, $C(O)NR^6R^7$, PO_3R^8, SO_3R^8, heterocyclic, OR^8, SH, $S(O)_nR^9$, NR^6R^7, $NH(CO)NR^6R^7$, $NH(CO)OR^9$, aryl or heteroaryl, said aryl or heteroaryl being optionally substituted by one or two groups independently selected from NR^6R^7, OR^8, $COOR^8$, SO_3R^8, $OCOR^8$, PO_3R^8, $C(O)NR^6R^7$ or heterocyclic;

Z is OR^{11}, $S(O)_nR^{11}$, $NR^{11}R^{12}$ or $CHR^{11}R^{12}$;

R^{11} and R^{12} are each independently hydrogen, C_1–C_7 alkyl, C_2–C_7 alkenyl, C_2–C_7 alkynyl or C_3–C_7 cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by $NR^{13}R^{14}$, $S(O)_nR^{13}$, OR^{13}, with the proviso that both R^{11} and R^{12} may not be hydrogen;

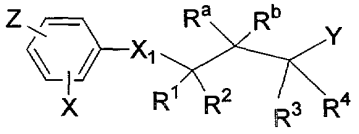
R^{13} and R^{14} are each independently H, $SiR^{15}R^{16}R^{17}$, C_1–C_7 alkyl, C_2–C_7 alkenyl, C_2–C_7 alkynyl, aryl or C_3–C_7 cycloalkyl, said alkyl, alkenyl, alkynyl, aryl or cycloalkyl group being optionally substituted by one to three groups independently selected from $COOR^8$, OR^8, Si $R^{15}R^{16}R^{17}$, OR^{15}, aryl, biaryl or heteroaryl, said aryl, biaryl or heteroaryl being optionally substituted with one to three groups independently selected from halogen, CF_3, OR^8, $COOR^8$, NO_2, or CN;

R^{13} and R^{14} when taken together may form a 5 –7 membered heterocyclic ring with one or more heteroatoms selected from O, N and S; said ring being optionally substituted by OR^8, $COOR^8$, or $C(O)NR^5R^6$;

R^{15}, R^{16}, R^{17} are each independently aryl, benzyl, benzhydryl, biaryl, heteroaryl, $(C_1$–$C_6)$ alkyl–aryl or $(C_1$–$C_6)$ alkyl–heteroaryl, said aryl radical

being optionally substituted by halogen, CF_3, OR^8, $COOR^8$, NO_2, CN, C_1-C_7 alkyl.

2. A compound of the formula



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or a pharmaceutically acceptable salt thereof wherein

X_1 is O, $S(O)_n$, $-\overset{R^5}{\underset{|}{N}}-$, $co-\overset{R^5}{\underset{|}{N}}-$ or $-CH_2-$, with the proviso that when X_1 is $-CH_2-$, R_1 and R_2 are only halogen.

n is 0, 1 or 2;

R^a and R^b when taken together form an oxo (=O) group, or R^a and R^b are each independently hydrogen, OH, $OCOR^9$, NH_2, N_3, $NHCOOR^9$, $NHCOCOR^9$, $NHSO_2R^9$ or F.

X is H, CF_3, OCF_3, halogen, C_1–C_7 alkyl, C_2–C_7 alkenyl, C_2–C_7 alkynyl or C_3–C_7 cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by $COOR^8$, CN, $C(O)NR^6R^7$, PO_3R^8, SO_3R^8, heterocyclic, OR^8, SH, $S(O)_nR^9$, NR^6R^7, $NH(CO)NR^6R^7$, $NH(CO)OR^9$, aryl or heteroaryl, said aryl or heteroaryl being optionally substituted by one or two groups independently selected from NR^6R^7, OR^8, $COOR^8$, SO_3R^8, $OCOR^9$, PO_3R^8, $C(O)NR^6R^7$ or heterocyclic;

R^1 and R^2 are each independently H, halogen, OR^9, C_1–C_7 alkyl, C_2–C_7 alkenyl, C_2–C_7 alkenyl or C_3–C_7 cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by $COOR^8$, CN, $C(O)NR^6R^7$, PO_3R^8, SO_3R^8, heterocyclic, OR^8, SH, $S(O)_nR^9$, NR^6R^7, $NH(CO)NR^6R^7$, $NH(CO)OR^9$, $OC(O)OR^9$, aryl or heteroaryl, said aryl or heteroaryl being optionally substituted with one or two groups independently selected from NR^6R^7, OR^8, $COOR^8$, SO_3R^8, $OCOR^9$, PO_3R^8, $C(O)NR^6R^7$ or heterocyclic;

R^3, R^4 and Y are each independently H, OR^{10}, $S(O)_nR^{10}$, C_1–C_7 alkyl, C_2–C_7 alkenyl, C_2–C_7 alkynyl or C_3–C_7 cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by $COOR^8$, CN, $C(O)NR^6R^7$, PO_3R^8, SO_3R^8, heterocyclic, OR^8, SH, $S(O)_nR^9$, NR^6R^7, $NH(CO)NR^6R^7$, $NH(CO)OR^9$, $OC(O)OR^9$, aryl or heteroaryl, said aryl or heteroaryl being optionally substituted by one or two groups independently selected from NR^6R^7, OR^8, $COOR^8$, SO_3R^8, $OCOR^8$, PO_3R^8, $C(O)NR^6R^7$ or heterocyclic;

R^5, R^6 and R^7 are each independently H, C_1–C_7 alkyl, C_2–C_7 alkenyl, C_2-C_7 alkynyl or C_3–C_7 cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by $COOR^8$, CN, OR^8, NR^8R^9, SO_3R^8, PO_3R^8, halogen, aryl or heteroaryl, said aryl or heteroaryl being optionally substituted by one or two groups independently selected from $COOR^8$, SO_3R^8, PO_3R^8 or heterocyclic;

R^8 is H, C_1–C_7 saturated straight chain alkyl or cycloalkyl, CF_3 or CH_2CF_3;

R^9 is same as R^8 but is not hydrogen;

R^{10} is C_1–C_7 alkyl, C_2–C_7 alkenyl, C_2–C_7 alkynyl or C_3–C_7 cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by $COOR^8$, CN, $C(O)NR^6R^7$, PO_3R^8, SO_3R^8, heterocyclic, OR^8, SH, $S(O)_nR^9$, NR^6R^7, $NH(CO)NR^6R^7$, $NH(CO)OR^9$, aryl or heteroaryl, said aryl or heteroaryl being optionally substituted by one or two groups independently selected from NR^6R^7, OR^8, $COOR^8$, SO_3R^8, $OCOR^8$, PO_3R^8, $C(O)NR^6R^7$ or heterocyclic;

Z is OR^{11}, $S(O)_nR^{11}$, $NR^{11}R^{12}$ or $CHR^{11}R^{12}$;

R^{11} and R^{12} are each independently hydrogen, C_1–C_7 alkyl, C_2–C_7 alkenyl, C_2–C_7 alkynyl or C_3–C_7 cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by $NR^{13}R^{14}$, $S(O)_nR^{13}$, OR^{13}, with the proviso that both R^{11} and R^{12} may not be hydrogen;

R^{13} and R^{14} are each independently H, $SiR^{15}R^{16}R^{17}$, C_1–C_7 alkyl, C_2–C_7 alkenyl, C_2–C_7 alkynyl, aryl or C_3–C_7 cycloalkyl, said alkyl, alkenyl, alkynyl, aryl or cycloalkyl group being optionally substituted by one to three groups independently selected from $COOR^8$, OR^8, Si $R^{15}R^{16}R^{17}$, OR^{15}, aryl, biaryl or heteroaryl, said aryl, biaryl or heteroaryl being optionally substituted with one to three groups independently selected from halogen, CF_3, OR^8, $COOR^8$, NO_2, or CN;

R^{13} and R^{14} when taken together may form a 5 – 7 membered heterocyclic ring with one or more heteroatoms selected from O, N and S; said ring being optionally substituted by OR^8, $COOR^8$, or $C(O)NR^5R^6$;

R^{15}, R^{16}, R^{17} are each independently aryl, benzyl, benzhydryl, biaryl, heteroaryl, (C_1–C_6) alkyl–aryl or (C_1–C_6) alkyl–heteroaryl, said aryl radical

being optionally substituted by halogen, CF_3, OR^8, $COOR^8$, NO_2, CN, or C_1–C_7 alkyl.

3. A compound of claim 2 wherein X_1 is O, or $S(O)_n$ and Y is OR^{10} in which R^{10} is C_1–C_7 alkyl, C_2–C_7 alkenyl, C_2–C_7 alkynyl or C_3–C_7 cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by $COOR^8$, CN, $C(O)NR^6R^7$, PO_3R^8, SO_3R^8, heterocyclic, OR^8, SH, $S(O)_nR^9$, NR^6R^7, $NH(CO)NR^6R^7$, $NH(CO)OR^9$, aryl or heteroaryl, said aryl or heteroaryl being optionally substituted by one or two groups independently selected from NR^6R^7, OR^8, $COOR^8$, SO_3R^8, $OCOR^9$, PO_3R^8, $C(O)NR^6R^7$ or heterocyclic, said R^6, R^7, R^8 and R^9 substituents being defined as in claim 2.

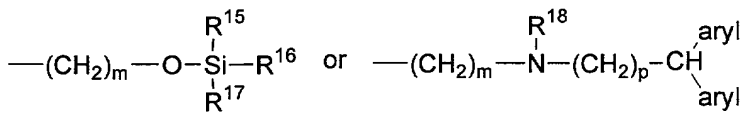
4. A compound of claim 3 in which R^a and R^b taken together represent an oxo (=O) group, or R^a and R^b are each independently hydrogen or OH.

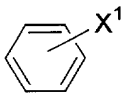
5. A compound of claim 3 wherein R^a and R^b are each independently hydrogen, $OCOR^9$, NH_2, N_3, $NHCOOR^9$ or $NHCOCOR^9$ in which R^9 is as defined in claim 2.

6. A compound of claim 4 wherein R^1 and R^2 are each independently halogen.

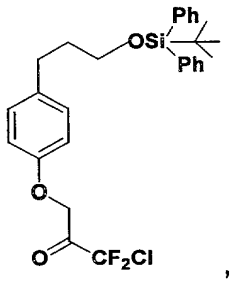
7. A compound of claim 3, 4, 5 or 6 in which

Z is



in which m and p each independently represent an integer of one to six, R^{15}, R^{16}, R^{17} are each independently C_1–C_7 alkyl, R^{18} is C_1–C_7 alkyl and aryl represents  in which X^1 is halogen.

8. A compound selected from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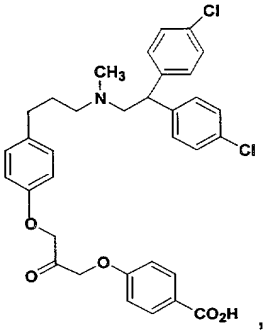
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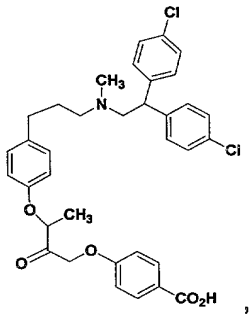
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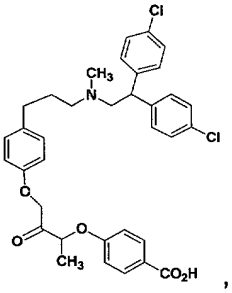
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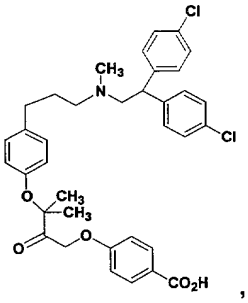
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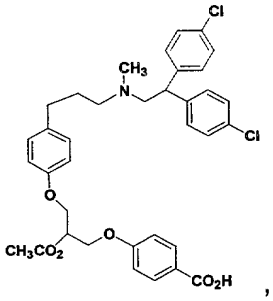
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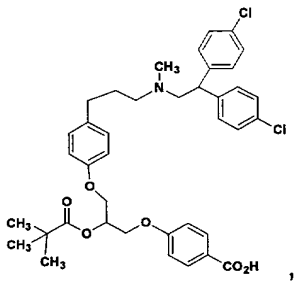
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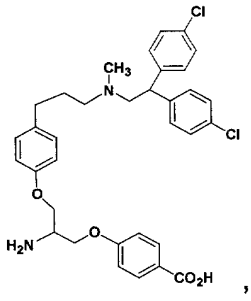
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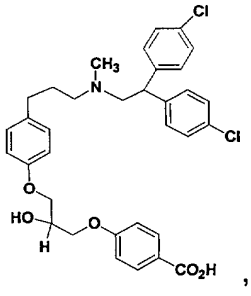
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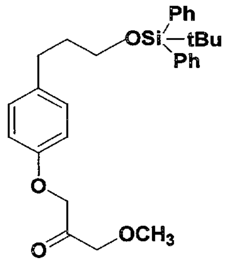
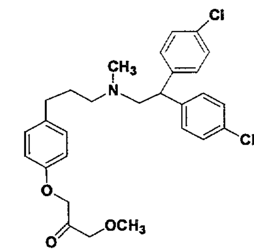
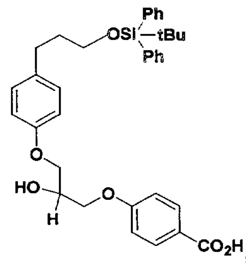
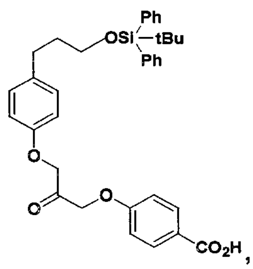
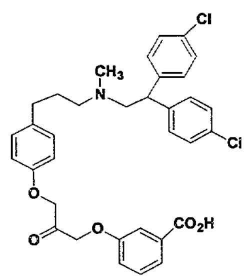
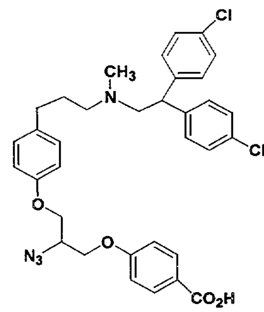
 ,

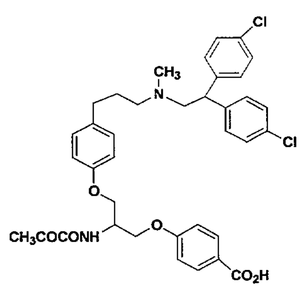
 ,

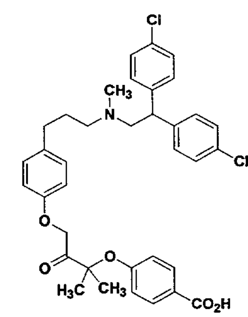


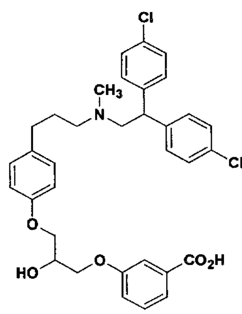


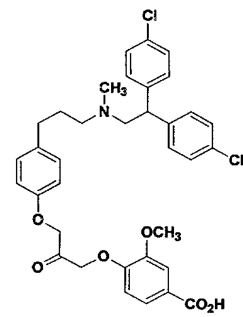
 ,

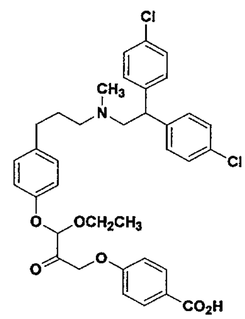
 ,

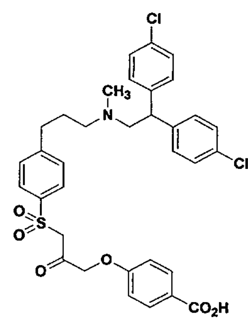


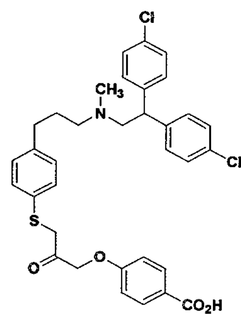
 ,

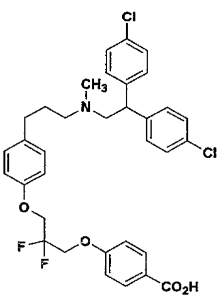
 ,

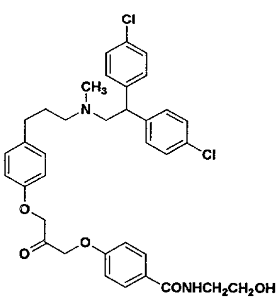
 ,

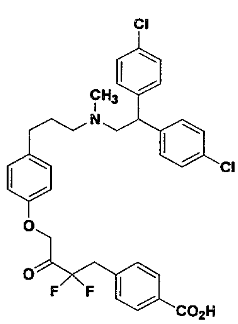
 ,

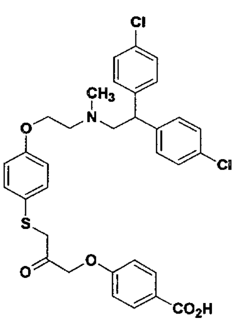
 ,

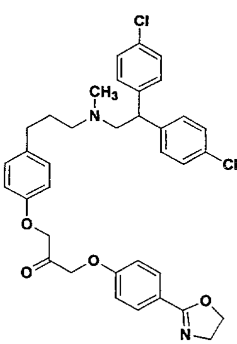
 ,

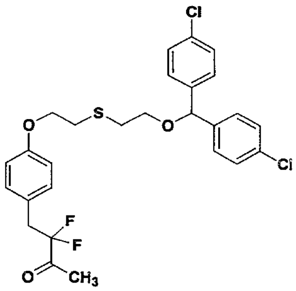
 ,

 ,

 ,

 ,

 ,



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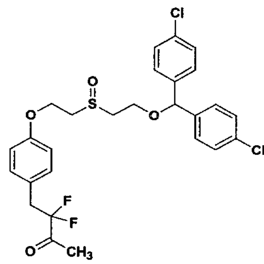

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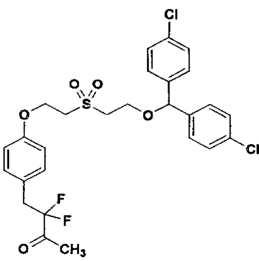

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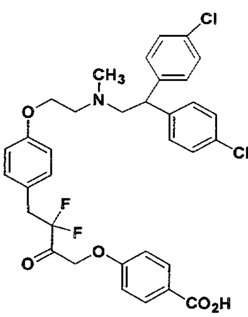

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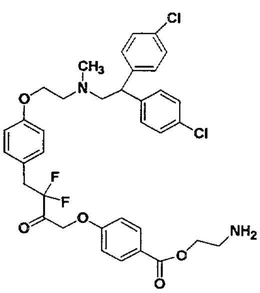

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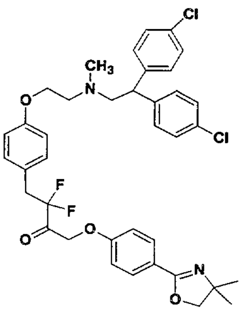

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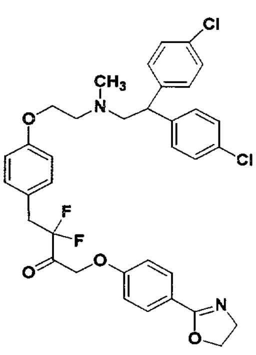

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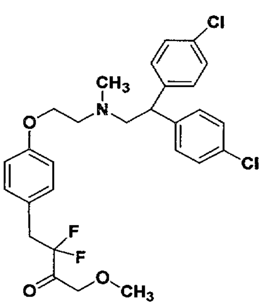

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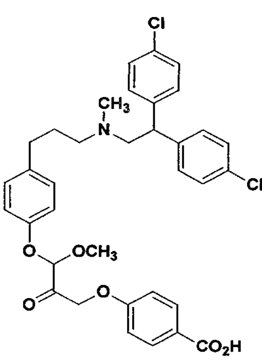

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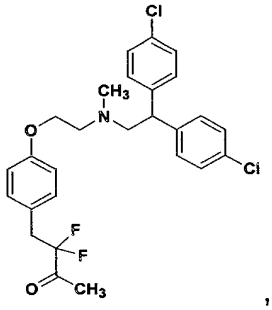

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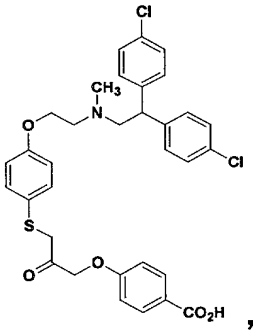

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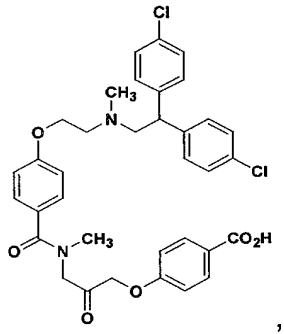

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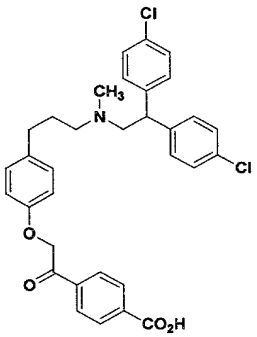

or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition for the inhibition of cytosolic phospholipase A_2 comprising a therapeutically effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

10. A method of inhibiting cytosolic phospholipase A_2 in a mammal in need thereof, comprising administering to said mammal a therapeutically effective amount of a compound of claim 1.